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PATENT SPECIFICATION

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807,620

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International Classification:—C07d.

COMPLETE SPECIFICATION

Manufacture of Indole Derivatives

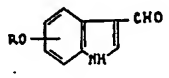
We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the manufacture of heterocyclic compounds and more particularly it relates to an improved process for the manufacture of certain derivatives of indole-3-aldehyde.

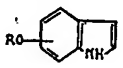
Certain methoxy- derivatives of indole-3-aldehyde have hitherto been obtained but only in very low yields and benzyloxy- derivatives of indole-3-aldehyde have not hitherto been obtained.

We have found an improved process for the manufacture of methoxyindole-3-aldehydes by which also there may be obtained the hitherto unknown benzoylindole-3-aldehydes.

According to the invention we provide a process for the manufacture of indole-3-aldehyde derivatives of the formula:—



wherein R stands for a methyl radical or a benzyl radical which comprises interaction of indole derivatives of the formula:—



wherein R has the meaning stated above, with dimethylformamide and either a phosphorus halide or a phosphorus oxyhalide, followed by decomposition of the intermediate product so formed, by heating in an alkaline medium.

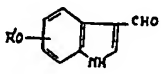
A preferred phosphorus oxyhalide is for example phosphorus oxychloride and preferred phosphorus halides are phosphorus tribromide and phosphorus pentachloride.

The process of the invention may conveniently be carried out in a suitable diluent or solvent for example dioxan. Alternatively, an excess of the dimethylformamide reactant may be used in place of a diluent or solvent. The preliminary formation of the intermediate product may be conveniently accelerated or completed by the application of heat. Suitable alkaline conditions for decomposition of the intermediate product may be for example an aqueous sodium hydroxide or an aqueous potassium hydroxide medium.

As examples of indole derivatives which may be used as starting materials in the process of the invention there may be mentioned 5-methoxyindole, 6-methoxyindole, 5-benzyloxyindole and 6-benzyloxyindole.

As stated the benzyloxyindole-3-aldehydes are new compounds.

Thus, according to a further feature of our invention we provide new compounds of the formula:—



wherein R^1 stands for a benzyl radical.

The indole-3-aldehyde derivatives made according to the process of this invention are useful as intermediates in the manufacture of pharmaceutically useful compounds, for example of 5-hydroxy-tryptamine.

The invention is illustrated but not limited by the following Examples in which the parts and percentages are by weight:—

EXAMPLE 1:

8.4 Parts of phosphorus oxychloride are added to 16 parts of dimethylformamide stirred at 10° to 20° C. A solution of 8.3 parts of 5-benzyloxyindole in 4 parts of dimethyl-

[*Price 3s. 6d.*]

formamide is then added at 20° to 30° C. The mixture is then heated at 35° C. during 45 minutes. It is then cooled and added to 100 parts of crushed ice. The mixture is stirred and a solution of 9.5 parts of sodium hydroxide in 50 parts of water is added slowly at 20° to 30° C. The rate of addition of the aqueous sodium hydroxide solution is such that 75% of the said solution is added during about 30 minutes whilst the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 2 minutes and then filtered. The solid residue is washed with cold water, dried and crystallised from ethanol. 5-benzyloxyindole-3-aldehyde is obtained of m.p. 237—238° C. in a yield of 85% calculated on the 5-benzyloxyindole used.

EXAMPLE 2:

5 Parts of phosphorus oxychloride are added to 10 parts of dimethylformamide at 10° to 20° C. To the mixture 4.33 parts of 6-methoxyindole in 5 parts of dimethylformamide are added at 20° to 30° C. The mixture is then heated at 35° to 40° C. during 45 minutes and is then poured into a mixture of 100 parts of ice and 50 parts of water. A solution of 8 parts of potassium hydroxide in 50 parts of water is added slowly at 15° to 20° C. at such a rate that when 75% of the said solution is added, the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 2 minutes, cooled and filtered and the solid residue is washed with water. The product so obtained is 6-methoxyindole-3-aldehyde of m.p. 187—189° C. in a yield of 83% calculated on the 6-methoxyindole used.

EXAMPLE 3:

5 Parts of phosphorus oxychloride are added to 15 parts of dimethylformamide at 10° to 20° C. To the mixture a solution of 4.3 parts of 5-methoxyindole in 5 parts of dimethylformamide is added at 20° to 30° C. The mixture is heated at 35° to 36° C. during 45 minutes and is then poured into a mixture of 100 parts of ice and 50 parts of water. A solution of 8 parts of potassium hydroxide in 50 parts of water is added slowly at 15° to 20° C. at such a rate that when 75% of the said solution is added, the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 5 minutes, cooled and filtered and the solid residue is washed with water. The product is 5-methoxyindole-3-aldehyde of m.p. 181—182° C. obtained in a yield of 94% calculated on the 5-methoxyindole used.

EXAMPLE 4:

8.4 Parts of phosphorus oxychloride are added dropwise with stirring to 18 parts of dimethylformamide cooled to 10° to 20° C. A solution of 10 parts of 6-benzyloxyindole in 4.5 parts of dimethylformamide is then added slowly at 20° to 30° C., after which the mixture is heated at 35° C. for 45 minutes. It is then cooled and poured into a mixture of 50 parts of crushed ice and 100 parts of water. A solution of 9.5 parts of sodium hydroxide in 100 parts of water is added slowly, with good stirring, at 20° to 30° C., the rate of addition of the aqueous sodium hydroxide is such that 75% of it is added during about 30 minutes and the mixture remains acid to litmus. The remaining 25% of the sodium hydroxide solution is then added all at once and the mixture is boiled for 5 minutes and then cooled to 50° to 55° C. and filtered. The solid residue is washed with cold water and dried when 6-benzyloxyindole-3-aldehyde of m.p. 208—209° C. is obtained in a yield of 90% calculated on the 6-benzyloxyindole used. It may be purified by crystallization from beta-ethoxyethanol when it has m.p. 215—216° C.

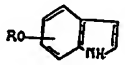
EXAMPLE 5:

14.3 Parts of phosphorus tribromide are added slowly to 18 parts of dimethylformamide with stirring, the temperature being maintained at 10° to 20° C. by external cooling. A solution of 5 parts of 6-benzyloxyindole in 9 parts of dimethylformamide is added slowly at 20° to 30° C. The mixture is then heated at 35° to 40° C. for 45 minutes with constant agitation. The reaction mixture is then poured into a mixture of 100 parts of ice and 100 parts of water, and to the mixture so obtained, is added a solution of 10 parts of sodium hydroxide in 100 parts of water, gradually during 30 minutes at 20° to 30° C. The alkaline solution is boiled for 5 minutes, cooled to 50° C. and filtered. The solid residue is washed with cold water and there is thus obtained 6-benzyloxyindole-3-aldehyde, m.p. 211—212° C. in a yield of 82% based on the 6-benzyloxyindole used. It may be purified by crystallization, for example, from beta-ethoxyethanol when it has m.p. 215—216° C.

EXAMPLE 6:

8.4 Parts of phosphorus oxychloride are added slowly at 10° to 20° C. to a stirred mixture of 20 parts of dioxan and 4.5 parts of dimethylformamide. A solution of 5 parts of 6-benzyloxyindole in 10 parts of dioxan is added gradually at 20° to 30° C. and the mixture is then warmed at 35° to 40° C. for 45 minutes. It is then poured into a mixture of 50 parts of ice and 100 parts of water. The stirred mixture is treated with a solution of 10 parts of sodium hydroxide in 100 parts of water, added at 20° to 30° C. during 30 minutes. The alkaline mixture is boiled for 5 minutes and then cooled to 50° C. and filtered. The solid residue is washed with cold water and dried and there is thus obtained 6-benzyl-oxyindole-3-aldehyde, m.p. 208° C. in a yield of 87% based on the 6-benzyloxyindole used. It may be purified by crystallization for example from beta-ethoxyethanol when it has m.p. 215—216° C.

wherein R stands for an alkyl radical or an aralkyl radical which comprises treating indole derivatives of the formula:—



wherein R has the meaning stated above, with dimethylformamide and either a phosphorus halide or a phosphorus oxyhalide.

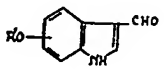
A preferred phosphorus oxyhalide is for example phosphorus oxychloride.

The process of the invention may conveniently be carried out in a suitable inert diluent or solvent. As suitable inert diluents or solvent for this purpose there may be used for example dimethylformamide and dioxan.

As examples of indole derivatives which may be used as starting materials in the process of the invention there may be mentioned 5-methoxyindole, 6-methoxyindole and 5-benzyloxyindole.

As stated the aralkyl-oxyindole-3-aldehydes are new compounds.

Thus, according to a further feature of our invention we provide new compounds of the formula:—



wherein R^1 stands for an aralkyl radical.

The indole-3-aldehyde derivatives made according to the process of this invention are useful as intermediates in the manufacture of pharmaceutically useful compounds, for example of 5-hydroxytryptamine.

The invention is illustrated but not limited by the following Examples in which the parts and percentages are by weight:—

EXAMPLE 1

8.4 Parts of phosphorus oxychloride are added to 16 parts of dimethylformamide stirred at 10° to 20°C. A solution of 8.3 parts of 5-benzyloxyindole in 4 parts of dimethylformamide is then added at 20° to 30°C. The mixture is then heated at 35°C. during 45 minutes. It is then cooled and added to 100 parts of crushed ice. The mixture is stirred and a solution of 9.5 parts of sodium hydroxide in 50 parts of water is added slowly at 20° to 30°C. The rate of addition of the aqueous sodium hydroxide solution is such that 75% of the said solution is added during about 30 minutes whilst the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 2 minutes and then filtered. The solid residue is washed with cold water, dried and crystallised from ethanol. 5-Benzyloxyindole-3-aldehyde is obtained of m.p. 237—238°C. in a yield of 85% calculated on the 5-benzyloxyindole used.

EXAMPLE 2

5 Parts of phosphorus oxychloride are added to 10 parts of dimethylformamide at 10° to 20°C. To the mixture 4.33 parts of 6-methoxyindole in 5 parts of dimethylformamide are added at 20° to 30°C. The mixture is then heated at 35° to 40°C. during 45 minutes and is then poured into a mixture of 100 parts of ice and 50 parts of water. A solution of 8 parts of potassium hydroxide in 50 parts of water is added slowly at 15° to 20°C. at such a rate that when 75% of the said solution is added, the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 2 minutes, cooled and filtered and the solid residue is washed with water. The product so obtained is 6-methoxyindole-3-aldehyde of m.p. 187—189°C. in a yield of 83% calculated on the 6-methoxyindole used.

EXAMPLE 3

5 Parts of phosphorus oxychloride are added to 15 parts of dimethylformamide at 10° to 20°C. To the mixture a solution of 4.3 parts of 5-methoxyindole in 5 parts of dimethylformamide is added at 20° to 30°C. The mixture is heated at 35°—36°C. during 45 minutes and is then poured into a mixture of 100 parts of ice and 50 parts of water. A solution of 8 parts of potassium hydroxide in 50 parts of water is added slowly at 15° to 20°C. at such a rate that when 75% of the said solution is added, the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 5 minutes, cooled and filtered and the solid residue is washed with water. The product is 5-methoxyindole-3-aldehyde of m.p. 181—182°C. obtained in a yield of 94% calculated on the 5-methoxyindole used.

WALTER SCOTT,
Agent for the Applicants.

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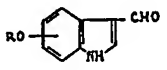
EXAMPLE 7:

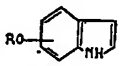
2 Parts of phosphorus pentachloride are added gradually with stirring to 18 parts of dimethylformamide maintained at 10° to 20° C. by external cooling. A solution of 1.5 parts of 6-benzyloxyindole in 4.5 parts of dimethylformamide is then added at 20° to 30° C. The temperature is then raised to 35° to 38° C. and held there for 45 minutes. The syrupy solution is then pouhed with good agitation into a mixture of 50 parts of ice and 100 parts of water and a solution of 5 parts of sodium hydroxide in 50 parts of water is then added during 20 minutes. The mixture is boiled for 10 minutes, cooled to about 50° C. and filtered. The solid residue is washed well with cold water and dried. The 6-benzyloxyindole-3-aldehyde thus obtained has m.p. 209° to 211° C., and is sufficiently pure for further use. It may be crystallized from beta-ethoxyethanol when the melting point is raised to 215° to 216° C.

WHAT WE CLAIM IS:—

1) Process for the manufacture of indole-3-aldehyde derivatives of the formula:—



wherein R stands for a methyl ralical or a benzyl radical which comprises treating indole derivatives of the formula:—



wherein R has the meaning stated above, with dimethylformamide and either a phosphorus halide or a phosphorus oxyhalide, followed by decomposition of the intermediate product so formed, by heating in an alkaline medium.

2) Process as claimed in Claim 1 wherein the phosphorus oxyhalide is phosphorus oxychloride.

3) Process as claimed in Claim 1 wherein the phosphorus halide is phosphorus tribromide or phosphorus pentachloride.

4) Process as claimed in Claims 1—3 wherein there is present a diluent or solvent for example dioxan.

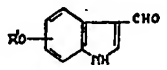
5) Process as claimed in Claims 1—3 wherein there is used an excess of the dimethylformamide reactant in place of a diluent or solvent.

6) Process as claimed in Claims 1—5 wherein the preliminary formation of the intermediate product is accelerated or completed by the application of heat.

7) Process as claimed in Claims 1—6 wherein the alkaline medium is an aqueous sodium hydroxide or an aqueous potassium hydroxide medium.

8) Process as claimed in Claims 1—7 wherein the indole derivatives used as starting materials are 5-methoxyindole, 6-methoxyindole, 5-benzyloxyindole or 6-benzyloxyindole.

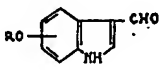
9) New compounds of the formula:—



wherein R^1 stands for a benzyl radical.

10) Process for the manufacture of indole-3-aldehyde derivatives, claimed in Claims 1—8, as hereinbefore particularly described and especially with reference to the foregoing Examples 1—7.

11) Indole-3-aldehyde derivatives of the formula:—



wherein R stands for a methyl radical wherever obtained by the process as claimed in Claims 1—8 or 10.

WALTER SCOTT,
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PROVISIONAL SPECIFICATION

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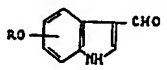
We have found an improved process for the manufacture of alkyloxyindole-3-aldehydes by which also there may be obtained the hitherto unknown aralkyl oxyindole-3-aldehydes.

According to the invention we provide a process for the manufacture of indole-3-aldehyde derivatives of the formula:—



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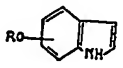

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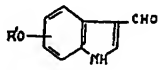

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EXAMPLE 3

5 Parts of phosphorus oxychloride are added to 15 parts of dimethylformamide at 10° to 20°C. To the mixture a solution of 4.3 parts of 5-methoxyindole in 5 parts of dimethylformamide is added at 20° to 30°C. The mixture is heated at 35°—36°C. during 45 minutes and is then poured into a mixture of 100 parts of ice and 50 parts of water. A solution of 8 parts of potassium hydroxide in 50 parts of water is added slowly at 15° to 20°C. at such a rate that when 75% of the said solution is added, the mixture is still acid and the remaining 25% of the said solution is then added all at once. The mixture is then boiled for 5 minutes, cooled and filtered and the solid residue is washed with water. The product is 5-methoxyindole-3-aldehyde of m.p. 181—182°C. obtained in a yield of 94% calculated on the 5-methoxyindole used.

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